

Satisfy Requirements for Residual Solvent Analysis

Agilent J&W DB-Select 624 Ultra Inert for <467>
and DB-WAX Ultra Inert capillary GC columns



Be Confident That Residual Solvents Will Not Affect the Safety, Stability, or Effectiveness of Your Products

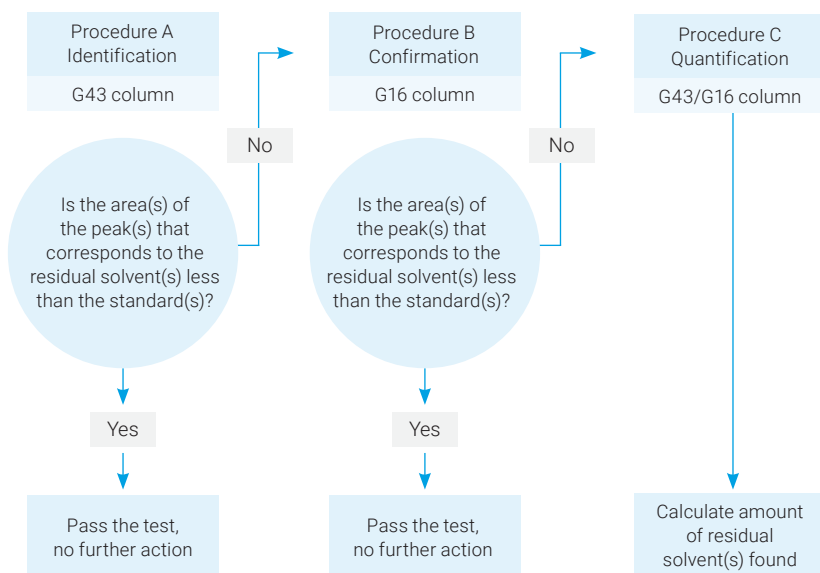
The manufacturing process for active pharmaceutical ingredients (APIs) may contribute to residual solvents remaining in the final product. Producers need to monitor and control the levels of residual solvents for several reasons—including safety, effect on crystalline form, solubility, bio-availability, and stability. Residual solvents can be classified* as follows:

- Class 1 solvents are considered hazardous, and should be avoided during manufacturing.
- Class 2 solvents are considered less severely toxic, and should be limited.
- Class 3 solvents pose less risk to human health than Class 1 or Class 2 solvents.

United States Pharmacopeia (USP) Method <467> is the method used worldwide for quality control, and closely follows ICH Q3C guidelines. The method is composed of three analytical procedures for identification and quantification.

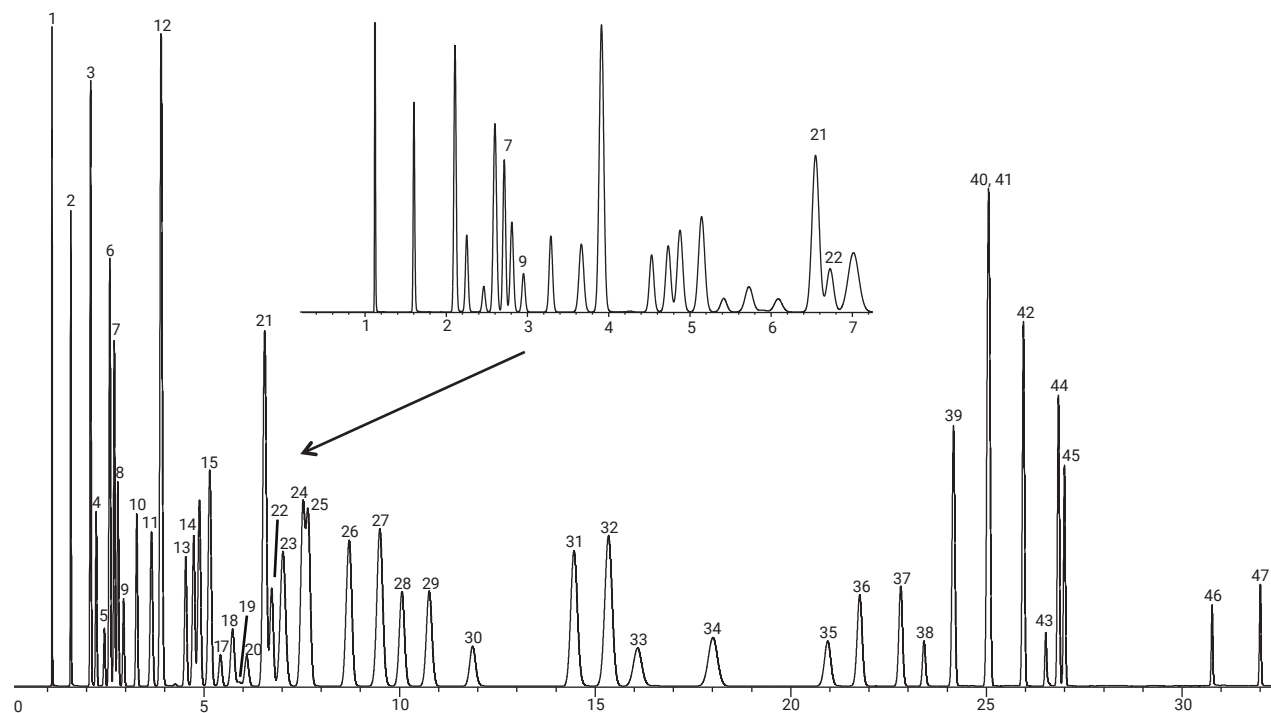
- Procedure A: Identification and limit testing. Uses a G43 phase (624-type column).
- Procedure B: Confirms whether an identified solvent is above the regulated limits. Uses a G16 phase (WAX-type column).
- Procedure C: Quantitative test using a G43 phase or G16 phase, depending on which produced fewer coelutions.

*Q3C—Tables and List Guidance for Industry, Rev 3, U.S. Department of Health and Human Services, CDER and CBER, FDA, June 2017.



USP <467> analytical flowchart for residual solvent analysis.

Elution of 46 USP <467> OVI solvents on a DB-Select 624 UI column (30 m x 0.53 mm id, 3.0 μm, part number 125-0334UI)



USP <467> requires columns to provide a resolution greater than 1.0 between acetonitrile and dichloromethane. The DB-Select 624 UI, 30 m megabore column has a resolution of 3.1 (see inset peaks 7 and 9). Benzene and 1,2-dichloroethane have a resolution of 1.1 (see inset peaks 21 and 22).

Conditions

Oven: 40 °C (20 min), 10 °C/min, 170 °C (0 min)
 Carrier gas: Helium 44 cm/s (approx. 6 mL/min) set at 40 °C, EPC-constant flow
 Inlet: Split, 5:1 at 250 °C (total flow approx 40 mL/min, and 4.5 psi)
 Detector: FID at 240 °C, H₂ @ 30 mL/min, air @ 400 mL/min, N₂ makeup @ 35 mL/min (constant column + makeup)
 Detector signal: 20 Hz
 Column serial number: USC9260355

1.120	Methane (1)*	5.180	Formic acid	14.665	Methyl isobutyl ketone (aka, 4-Methyl-2-pentanone, MIBK)
1.603	Methanol (2)	5.223	Tetrahydrofuran (THF)	15.330	Toluene (32)
2.092	n-Pentane	5.408	Chloroform (17)	16.126	3-Methy-1-butanol (33)
2.111	Ethanol (3)	5.721	1,1,1-Trichloroethane (18)	18.017	Isobutyl acetate (34)
2.256	Diethyl ether (4)	5.889	Cyclohexane (19)	20.985	1-Pentanol (35)
2.458	1,1-Dichloroethylene (5)	6.079	Carbon tetrachloride (20)	21.776	Methyl-butyl-ketone (MBK) (36)
2.472	Acetone	6.471	2-Methoxyethanol	22.822	n-Butyl acetate (37)
2.597	2-Propanol (6)	6.540	2-Methylpropanol	23.430	N,N-Dimethylformamide (38)
2.635	Ethyl formate	6.560	Benzene (21)	24.162	Chlorobenzene (39)
2.713	Acetonitrile (7)	6.719	1,2-Dichloroethane (22)	25.024	m-Xylene (40)
2.807	Methyl acetate (8)	6.982	Isopropyl acetate	25.024	p-Xylene (41)
2.955	Dichloromethane (9)	7.015	Isooctane (2,2,4-Trimethylpentane) (23)	25.950	o-Xylene (42)
3.285	trans-1,2-Dichloroethylene (10)	7.539	3-Methyl-2-butanone (24)	26.526	Dimethyl sulfoxide (43)
3.285	Methyl-t-butyl ether (MTBE)	7.652	n-Heptane (25)	26.839	Cumene (44)
3.662	n-Hexane (11)	7.770	Acetic acid	26.872	N,N-Dimethylacetamide
3.917	1-Propanol (12)	8.624	Trichloroethylene (26)	27.020	Anisole (45)
3.930	Isopropyl ether (DIPE)	8.675	1-Butanol	30.775	N-Methyl pyrrolidone (46)
4.534	Nitromethane (13)	9.490	Methycyclohexane (27)	30.807	Formimide
4.730	cis-1,2-Dichloroethylene (14)	10.066	1,4-Dioxane (28)	32.005	Tetralin (47)
4.733	2-Butanone	10.767	Propyl acetate (29)		
4.877	Ethyl acetate (15)	11.922	2-Ethoxyethanol (30)		
5.163	2-Butanol (16)	14.518	Pyridine (31)		

*Numbers in italics are the peak ID numbers for the chromatogram.

USP <467> Procedure A

High repeatability for
identification and limit testing



Procedure A is the first step in the identification process. It is performed on a G43 phase (624-type column) to determine whether residual solvents are present at detectable levels.

Single-column GC/FID analysis of residual solvents

In this example, Agilent J&W DB-Select 624 UI columns delivered excellent resolution of the residual solvent peaks. The Agilent 7697A headspace sampler was also a key factor in achieving the lower limits of concentration for these tests. Its inert sample path, thermal zone stability, and flexible EPC-controlled vial sampling all contribute to reliable system performance.

Conditions

Column:	Agilent J&W DB-Select 624 UI for <467>, 30 m x 0.32 mm, 1.8 µm (p/n 123-0334UI)
Carrier:	Helium, 2.2 mL/min constant flow at 40 °C
Oven:	40 °C (20 min), then 10 °C/min to 240 °C (5 min)
Inlet:	MMI, 140 °C, 1 µL split 5:1
Sample vol:	1.0 mL loop
FID:	250 °C, H ₂ @ 30 mL/min, air @ 400 mL/min, N ₂ constant col + makeup = 30 mL/min

Flow path supplies

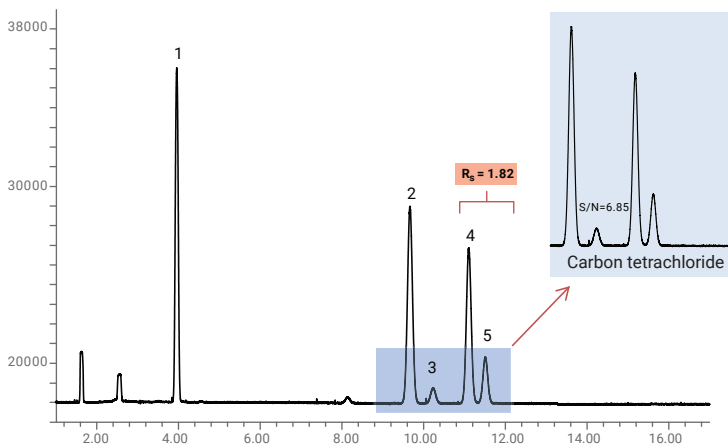
Vials:	20 mL Flat bottom crimp cap headspace vials (100 pk, p/n 5190-2288)
Vial caps:	Headspace crimp cap /high performance septa (100 pk, 5190-3987)
Crimper:	Electronic crimper for 20 mm caps (p/n 5191-5615)
Transfer line:	0.53 mm deactivated fused silica (5 m, p/n 160-2535-5)
Fitting:	1/6 to 1/32 inch reducing fitting (p/n 0100-2594)
Septum:	Non-stick, bleed and temperature optimized (50 pk, p/n 5183-4757)
Inlet liner:	1 mm straight single taper Ultra Inert liner (p/n 5190-4047)
Gold seal:	Gold plated inlet seal with washer (10/pk, p/n 5190-2209)
Ferrules:	0.5 mm id short 85/15 Vespel/graphite (10 pk, p/n 5062-3514)
Magnifier:	20x Magnifier loop (p/n 430-1020)

Standards

Class 1:	USP <467> class 1 residual solvents (p/n USPM-467J-1)
Class 2A:	USP <467> class 2 residual solvents A (p/n USPM-467K-1)
Class 2B:	USP class 2 residual solvents B (p/n USPM-467L-1) USP class 2 residual solvents B, low (p/n USPM-467N-1) USP <467> class 2B, low (p/n 5190-0513)
Class 2C:	USP <467> class 2 residual solvents C (p/n USPM-467M-1)
USP <467> calibration standards:	USPM-467A-1, USPM-467C-1, USPM-467D-1

These chromatograms represent all three solvent classes tested using Procedure A. Excellent peak shape was achieved by combining Agilent J&W DB-Select 624 UI columns with the Agilent 7697A headspace sampler.

Class 1

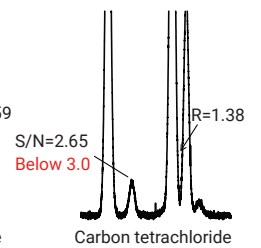
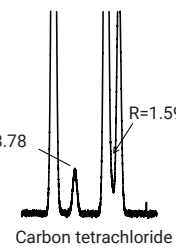
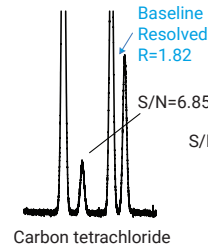


1. 1,1-Dichloroethene
2. 1,1,1-Trichloroethane
3. Carbon tetrachloride
4. Benzene
5. 1,2-Dichloroethane

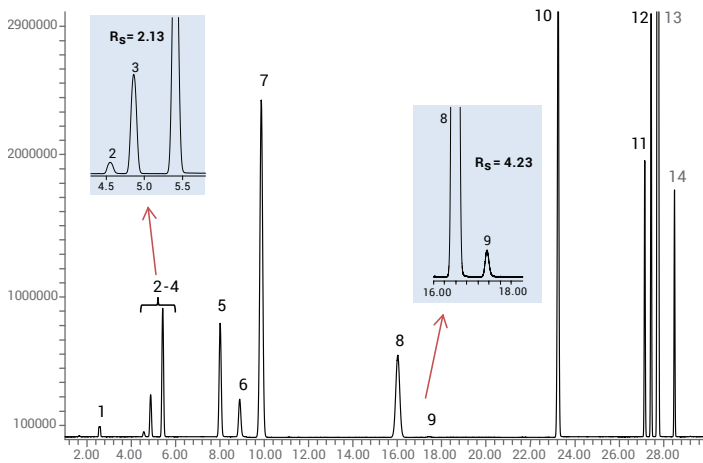
DB-Select 624 UI <467>

Vendor X G43

Vendor Y G43



Class 2A



1. Methanol
2. Acetonitrile
3. Dichloromethane
4. *trans*-1,2-Dichloroethene
5. *cis*-1,2-Dichloroethene

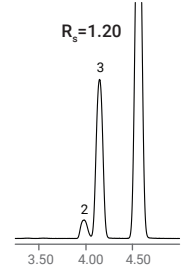
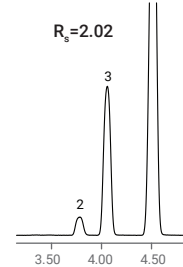
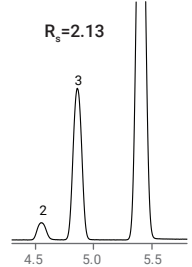
6. Tetrahydrofuran
7. Cyclohexane
8. Methylcyclohexane
9. 1,4-Dioxane
10. Toluene

11. Chlorobenzene
12. Ethylbenzene
13. *m-p*-Xylene
14. *o*-Xylene

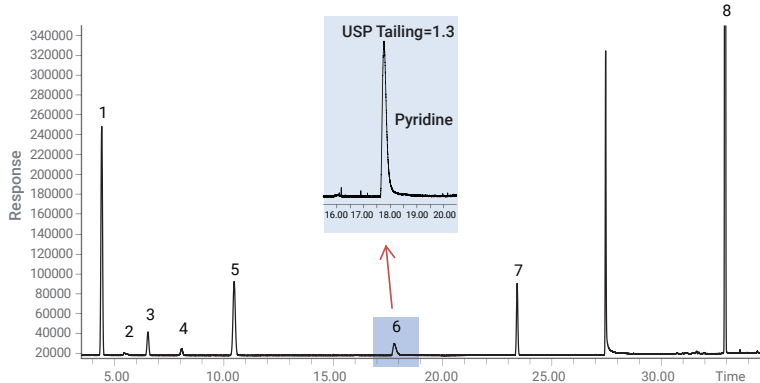
DB-Select 624 UI <467>

Vendor X G43

Vendor Y G43



Class 2B



1. Hexane
2. Nitromethane
3. Chloroform

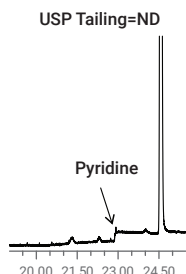
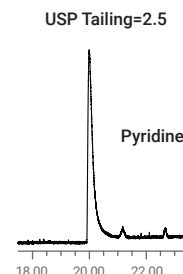
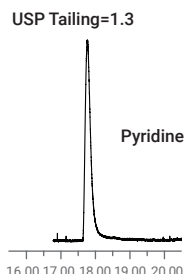
4. 1,2-Dimethoxyethane
5. Trichloroethylene
6. Pyridine

7. 2-Hexanone
8. Tetralin

DB-Select 624 UI <467>

Vendor X G43

Vendor Y G43



Class 1 (top), class 2A (middle), and class 2B (bottom) solvents at USP <467> limit concentrations.

For more information, refer to application note 5991-0616

USP <467> Procedure B

Excellent chromatographic performance for confirmatory testing



Once a residual solvent is identified and determined to be above the daily exposure limit, Procedure B is performed to confirm analyte identity.

Single-column GC/FID analysis of residual solvents

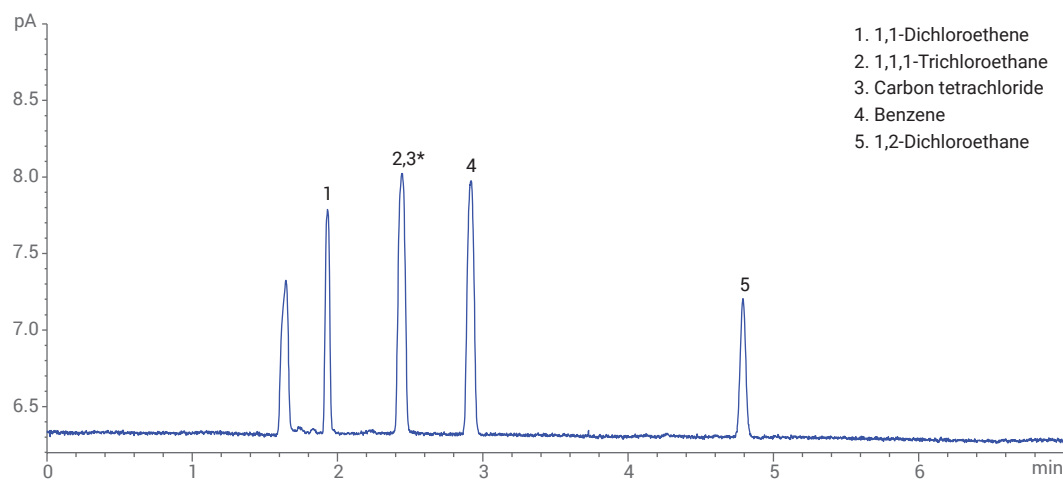
Here, USP <467> Procedure B was used to confirm the peak identification of Procedure A. An Agilent J&W DB-WAX UI GC column was used as a confirmation column.

Conditions

GC system:	Agilent 7890B	FID:	250 °C
Column:	Agilent J&W DB-WAX UI, 30 m × 0.32 mm, 0.25 µm (p/n 123-7032UI)	Headspace:	Agilent 7697A headspace sampler
Liner:	Agilent liner, splitless, straight, deactivated, quartz (p/n 5181-8818) Equivalent: Agilent Ultra Inert liner, splitless, straight, 1 mm id (p/n 5190-4047)	Oven temperature:	80 °C
Inlet:	Split/splitless, 140 °C, split ratio 5:1	Loop temperature:	80 °C
Oven:	50 °C (hold 20 min) to 165 °C at 6 °C/min (hold 20 min)	Transfer line temperature:	100 °C
		Equilibration time:	45 min
		Sample loop:	1 mL

The Agilent J&W DB-WAX UI GC column demonstrated good resolution, peak shape, sensitivity, and repeatability for the three classes of residual solvents at method-specified limits.

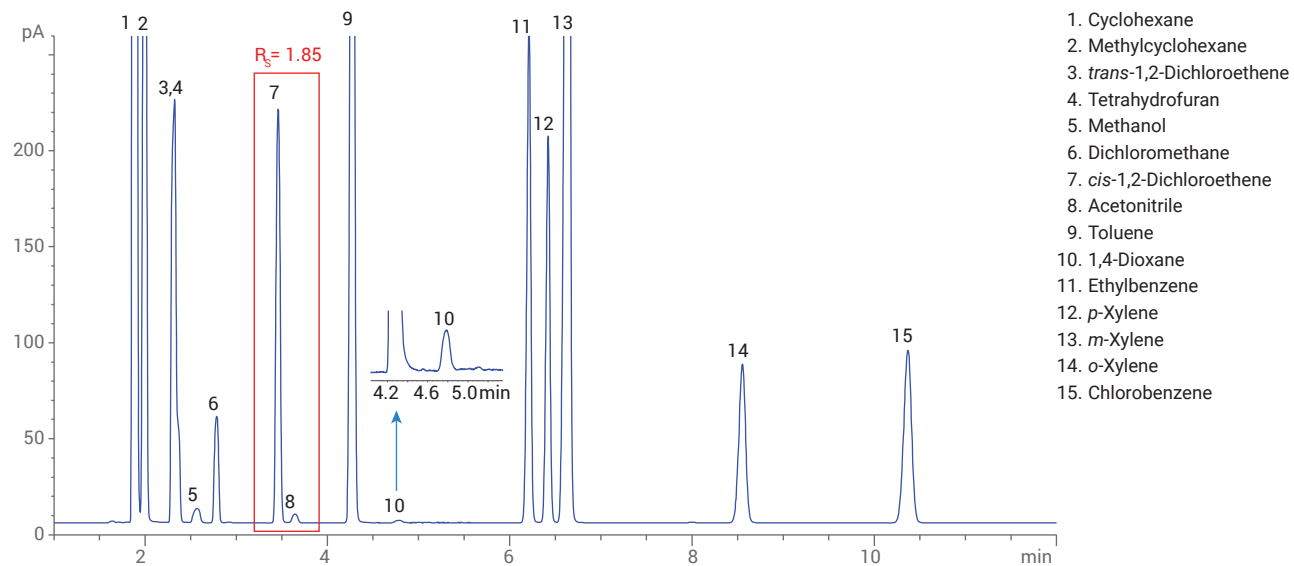
Class 1



Class 1 standard solution resolved on an Agilent J&W DB-WAX Ultra Inert GC column.

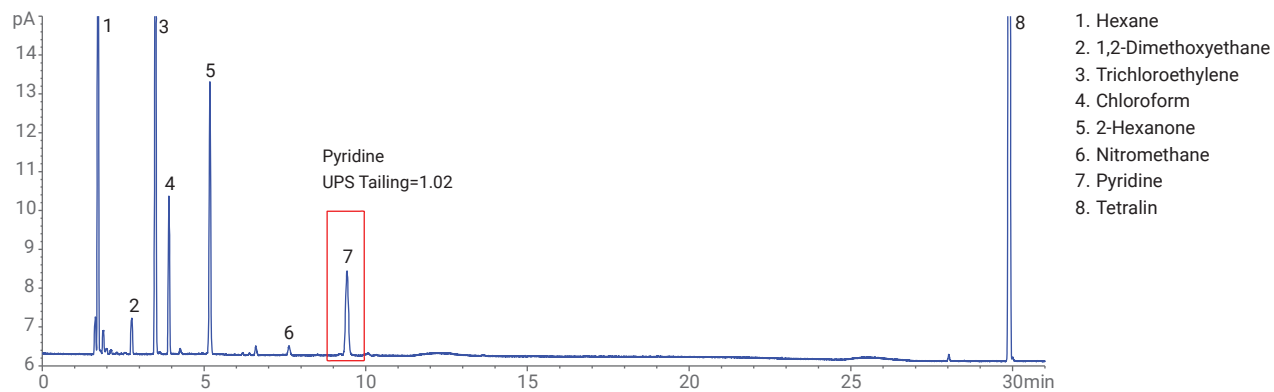
*Carbon tetrachloride coelutes with 1,1,1-Trichloroethane with the G16 column, but is separated from all peaks in the class 1 standard with the G43 column.

Class 2A



Class 2A standard solution resolved on an Agilent J&W DB-WAX Ultra Inert 30 m × 0.32 mm, 0.25 μm GC column.

Class 2B



Class 2B standard solution resolved on an Agilent J&W DB-WAX Ultra Inert 30 m × 0.32 mm, 0.25 μm GC column.

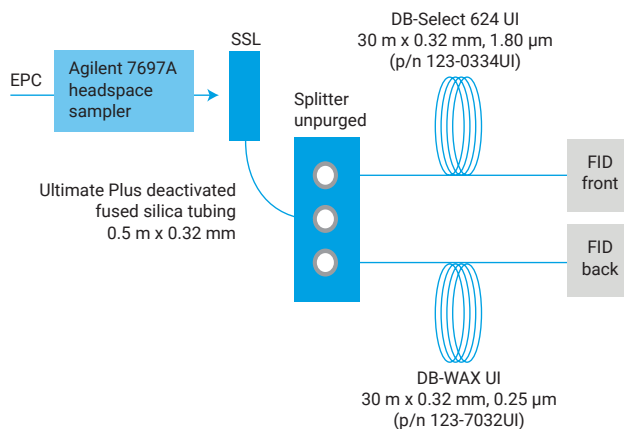
Dual-column GC/FID analysis of residual solvents

With the dual-channel GC/FID configuration, static headspace analysis performed at 85 °C for 40 minutes improved repeatability and reduced analysis time and cycle time. A DB-WAX UI GC column was used as a confirmation column in this system. USP <467> procedures A and B can be accomplished in one run with the dual-channel configuration.

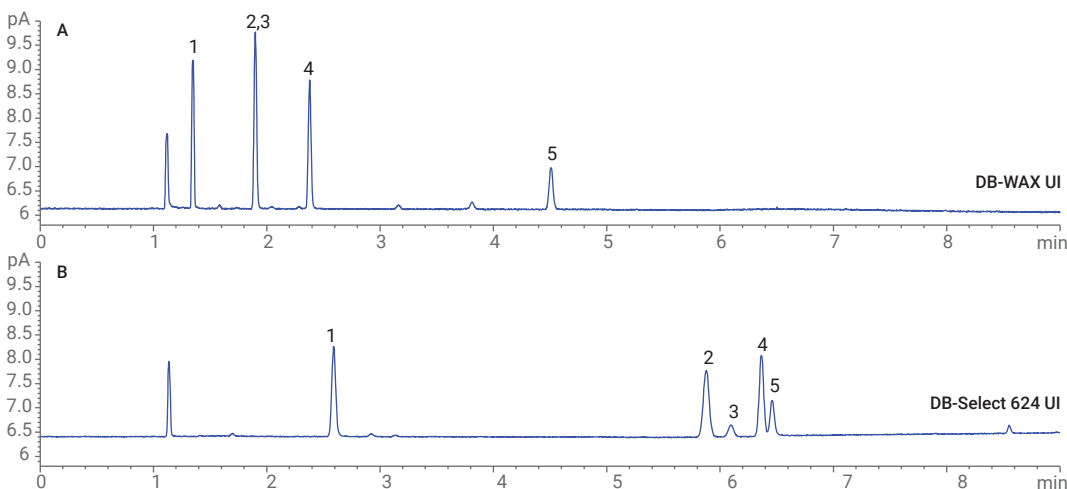
Conditions

GC system:	Agilent 7890B
Column 1:	Agilent J&W DB-WAX UI, 30 m × 0.32 mm, 0.25 μm (p/n 123-7032UI)
Column 2:	Agilent J&W DB-Select 624 UI, 30 m × 0.32 mm, 1.8 μm (p/n 123-0334UI)
Liner:	Agilent liner, splitless, straight, deactivated, quartz (p/n 5181-8818) Equivalent: Agilent Ultra Inert liner, splitless, straight, 1 mm id (p/n 5190-4047)
Tubing:	Agilent Ultimate Plus deactivated fused silica tubing, 0.5 m × 0.32 mm (p/n CP803205)
Carrier gas:	Helium, constant flow mode, 15 psi
Inlet:	Split/splitless, 140 °C, split ratio 2.5:1
Oven:	40 °C (hold 5 min) to 240 °C at 18 °C/min (hold 2 min)
FID (both channels):	250 °C
Headspace:	Agilent 7697A headspace sampler
Oven temperature:	85 °C
Loop temperature:	85 °C
Transfer line temperature:	100 °C
Equilibration time:	40 min
Sample loop:	1 mL

Dual-channel GC/FID system



Class 1

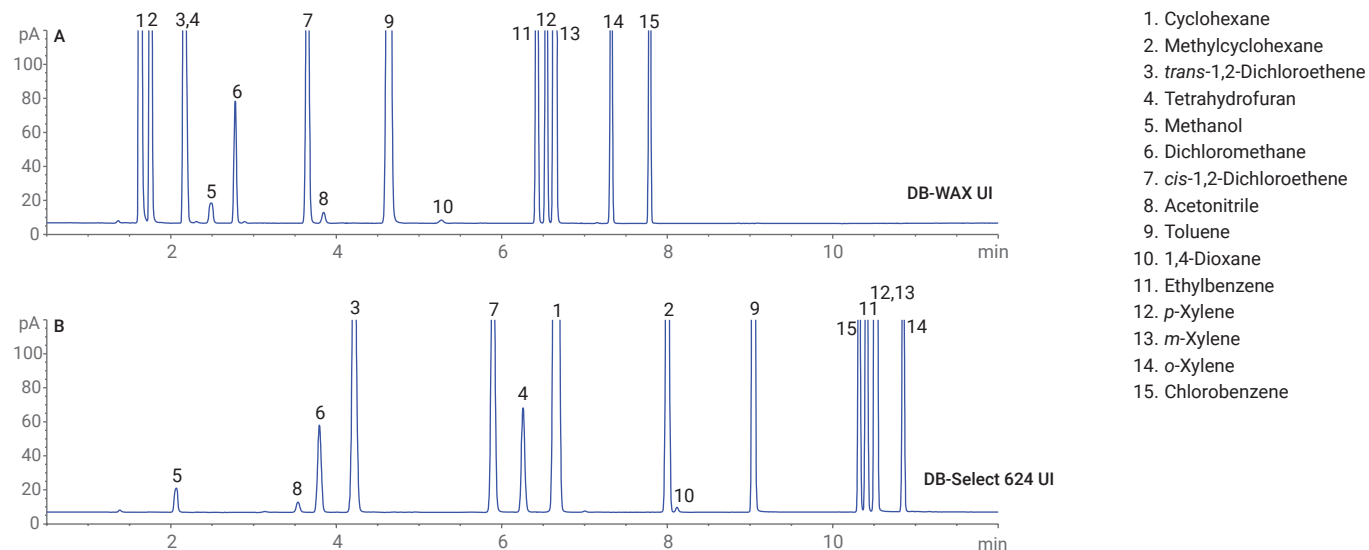


- 1,1-Dichloroethene
- 1,1,1-Trichloroethane
- Carbon tetrachloride
- Benzene
- 1,2-Dichloroethane

Class 1 standard solution analyzed using an Agilent J&W DB-WAX UI and an Agilent DB-Select 624 UI GC column.

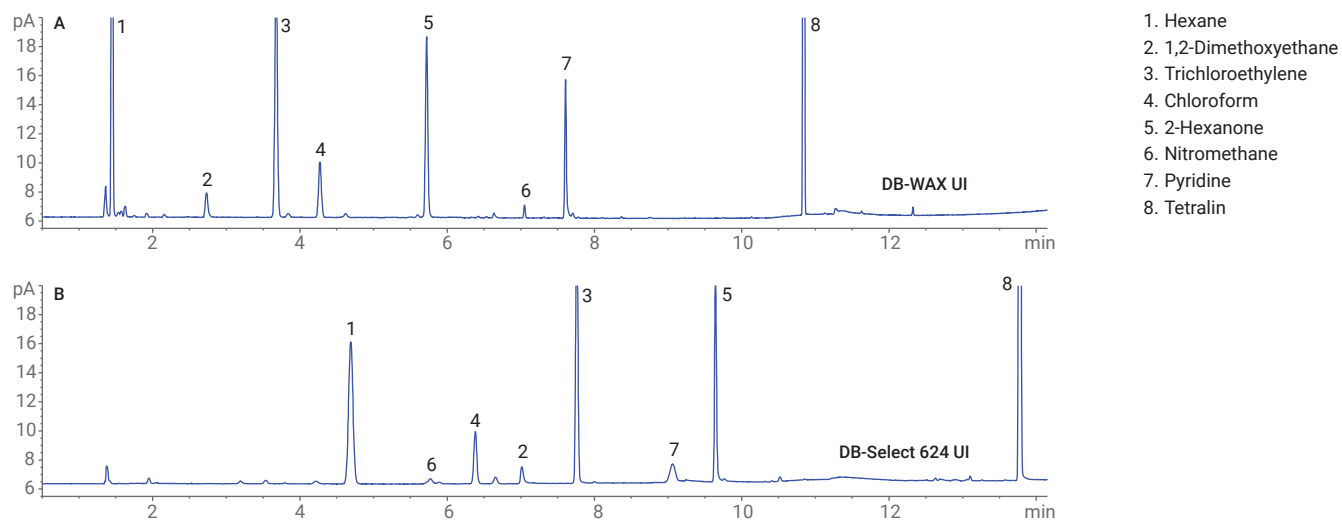
The high inertness of the DB-WAX UI column provided excellent peak shape for residual solvents. For pyridine—a particularly challenging compound—USP tailing was 1.06.

Class 2A



Class 2A standard solution analyzed using an Agilent J&W DB-WAX UI and an Agilent DB-Select 624 UI GC column.

Class 2B



Dual-channel GC/FID chromatograms of class 2B standard solution using an Agilent J&W DB-WAX UI and an Agilent DB-Select 624 UI GC column.

USP <467> Procedure Summary

Proven resolution, peak shape, and sensitivity

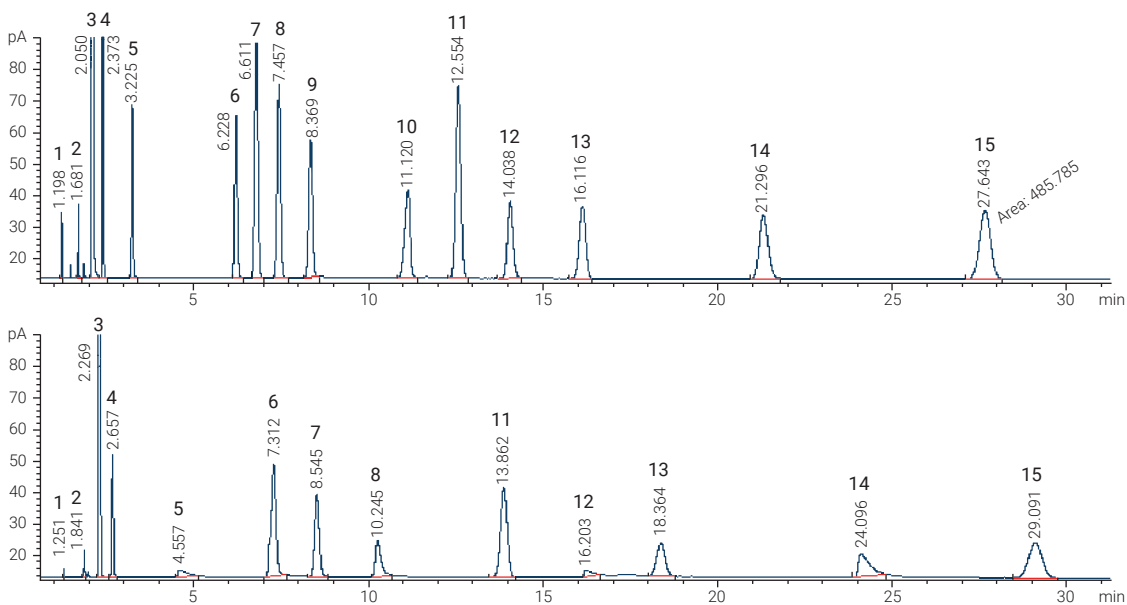


Agilent J&W DB-Select 624 UI columns showed excellent performance for residual solvent analysis according to USP <467> Procedure A. Repeatability was generally better than 2.5% RSD for Class 1, Class 2A, and Class 2B solvents.

Once a residual solvent was identified above the permitted daily exposure (PDE) limit, Procedure B was performed to confirm analyte identity. The Agilent J&W DB-WAX UI GC column was successfully used as a confirmation column, because it yields an alternate selectivity compared to that of a G43 column.

Comparison: Agilent versus the competition

These chromatograms compare an Agilent DB-Select 624 UI (30 m x 0.53 mm x 3.0 μm) with a column from Brand Z (30 m x 0.53 mm x 3.0 μm).



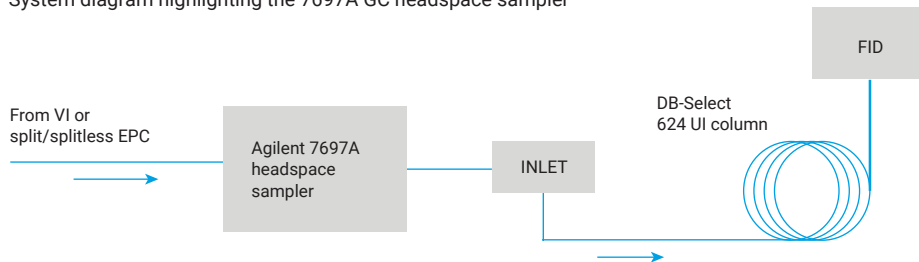
1. Methane
2. Methanol
3. Ethanol
4. 1-Propanol
5. Acetic acid
6. Pyridine
7. Octane
8. 1-Pentanol
9. 1,2-Propanediol
10. n-Butyric acid
11. m-Xylene
12. 4-Methylpyridine
13. Bromoform
14. Dimethyl methylphosphonate
15. Decane

First-class precision, reliability, and ease of use: Agilent 7697A GC headspace sampler

With best-in-class technology and powerful software, the Agilent 7697A headspace sampler is packed with the latest productivity-boosting features.

- Unique sampling design allows you to use hydrogen as a carrier gas, delivering optimal chromatography and helping to future-proof your lab.
- Comprehensive software goes beyond sample handling to guide you through tasks such as method development and resource conservation.
- Method optimization tools facilitate headspace method development.
- Electronic pneumatic control, vial leak checking, and barometric pressure compensation ensure consistent results.

System diagram highlighting the 7697A GC headspace sampler



Agilent-engineered GC supplies deliver what your pharmaceutical applications demand

Make productivity happen with the Agilent ADM Flow Meter

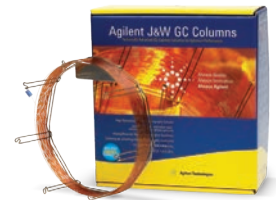
The ADM Flow Meter measures volumetric gas flow, and is a valuable tool for troubleshooting detector problems.

Visit www.agilent.com/chem/admflowmeter

Protect the purity of your gas with the Agilent Gas Clean filter

Inserting a Gas Clean filter system in the gas line immediately before the instrument inlet greatly reduces the level of contaminants and impurities, improving trace analysis.

Visit www.agilent.com/chem/gasclean



Residual Solvent Analyzers

Streamline your USP <467>
residual solvent detection



Based on the Agilent Intuvo 9000 GC system, Agilent Residual Solvent Analyzers are factory pretested and preconfigured to deliver results, *fast*, while saving precious startup time. What's more, their analytical precision exceeds USP method requirements for the three classes of residual solvents.

Facilitate your QA/QC with these unique advantages

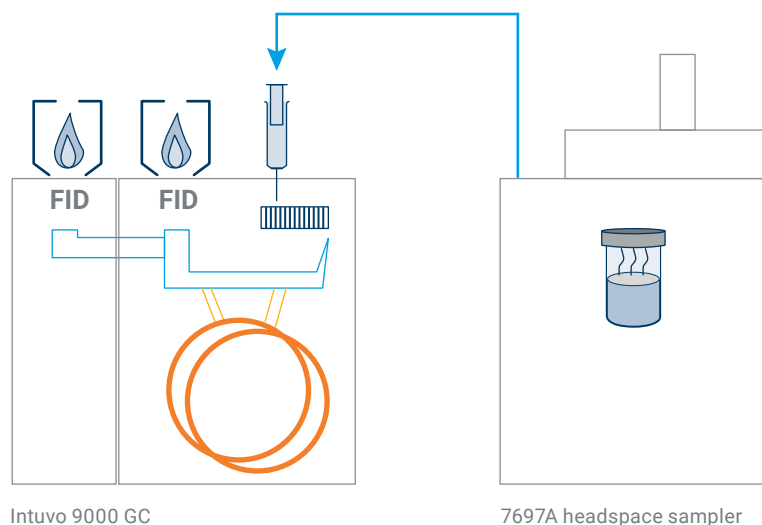
- Preconfigured to meet system suitability requirements for USP <467>, including column, consumables, calibration/checkout samples, and analytical method.
- Chemically tested to ensure optimal analysis of class 1 and class 2A/B solvents.
- Precise temperature and sampling control routines. The Agilent 7697A headspace sampler maximizes throughput and minimizes operator error.
- Headspace thermal zone stability of ± 0.1 °C, inert flow path, and capillary flow technology provide excellent RSD for class 1 and 2A/B solvents—while minimizing carryover.
- Begin system calibration and validation immediately following installation.



Easily quantitate OVI content with dual-FID residual solvent analyzers

Dual-FID analyzers are ideal for identifying organic contaminants in active ingredients, formulations, and additives. The dual-FID configuration uses dissimilar columns for added confirmation within a single injection.

In addition, an inert sample flow path and thermal zone stability—combined with the automation capabilities of the Agilent 7697A headspace sampler—provide unsurpassed accuracy and repeatability.



Intuvo 9000 GC

7697A headspace sampler

Intuvo residual solvent analyzers reflect innovative technology and a stringent quality control process

Systems include:

Factory

- System assembly, performance check, and leak testing
- Application, configuration, and Agilent J&W Ultra Inert columns
- Factory chemical performance verification with application-specific chemical checkout mix

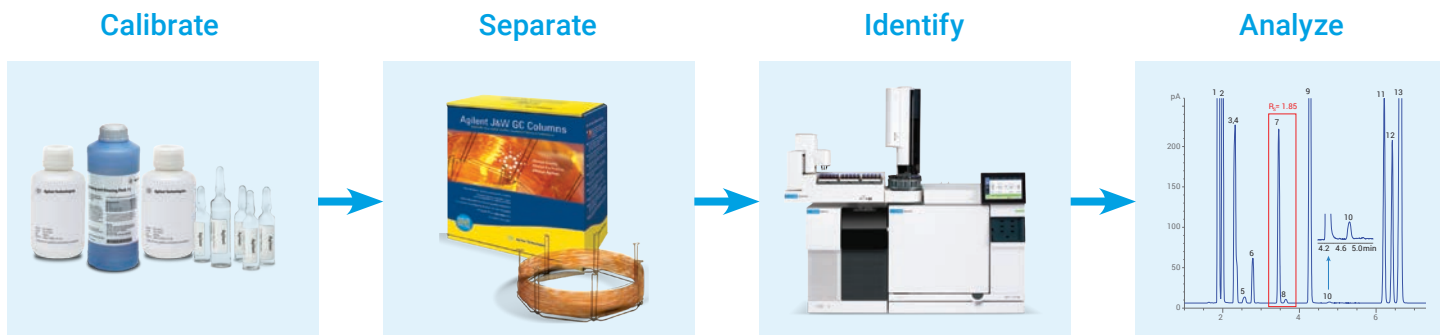
Delivery

- DVD with method parameters and checkout data files for easy out-of-the-box operation
- Instrument and method operational manuals
- Information to help you reorder consumables easily

Installation

- Onsite installation by factory-certified support engineer
- Duplicate factory checkout with application-specific class 2A checkout sample
- Optional application startup assistance

Achieve USP <467> Compliance with the Complete Agilent Residual Solvents Workflow



Ordering information

Use our new “My List” links to simplify ordering.

This table will help you choose the consumables you will need for your USP <467> analysis. Clicking on the “[GC columns and supplies for 7890/8890 systems](#)” or “[GC columns and supplies for Intuvo systems](#)” will add all the USP <467> consumables for your specific GC system to “My Favorites”. Select the items and quantities you need and add them to the Agilent Online Store* shopping cart.

Alternatively, clicking on the header links will place only the items listed underneath the header in “My Favorites”. You can add or remove items from the shopping cart to suit your needs.

GC columns and tubings for 7890/8890 GC systems

USP <467> Single-Column GC/FID Analysis of Residual Solvents

Column for Procedure A: Identification and limit testing

Agilent J&W DB-Select 624 UI for <467>, 30 m × 0.32 mm, 1.8 μm 123-0334UI

Column for Procedure B: Confirmatory testing

Agilent J&W DB-WAX UI, 30 m × 0.32 mm, 0.25 μm 123-7032UI

USP <467> Dual-Column GC/FID Analysis of Residual Solvents

Agilent J&W DB-WAX UI, 30 m × 0.32 mm, 0.25 μm 123-7032UI

Agilent J&W DB-Select 624 UI for <467>, 30 m × 0.32 mm, 1.8 μm 123-0334UI

Agilent Ultimate Plus deactivated fused silica tubing, 0.5 m × 0.32 mm . . . CP803205

GC columns for the Intuvo 9000 GC system

Procedure A

J&W DB-Select 624 Ultra Inert Intuvo GC column module,
30 m, 0.32 mm, 1.8 μm 123-0334UI-INT

Procedure B

J&W DB-WAX Ultra Inert Intuvo GC column module,
30 m, 0.32 mm, 0.25 μm 123-7032UI-INT

GC supplies for the Intuvo 9000 GC system

Guard chip, Intuvo, split/splitless inlet, 2/pk G4587-60565

Gasket, Intuvo, polyimide, 5/pk 5190-9072

Flow chip, Intuvo, inlet G4581-60031

Flow chip, Intuvo, D1 G4581-60032

**If this is your first time using the Agilent Online Store, you will be asked to enter your email address for account verification. If you don't have a registered Agilent account, you will need to [register](#) for one. The “My List” feature is valid only in regions that are e-commerce enabled. All items can also be ordered through your regular sales and distributor channels.*

Not available in all countries. Please contact your local sales representative for availability.



GC liners for USP <467>

Agilent liner, splitless, straight, deactivated, quartz	5181-8818
1 mm straight single taper Ultra Inert liner (equivalent) recommended	5190-4047

GC inlet parts and other supplies

Gold plated inlet seal with washer, 10/pk*	5190-2209
Gold plated inlet seal with washer, Ultra Inert, 10/pk (recommended)*	5190-6145
Gold plated inlet seal with washer, Ultra Inert, 50/pk*	5190-6149
Non-stick, bleed and temperature optimized, 11 mm, 50/pk	5183-4757
Non-stick, bleed and temperature optimized, 11 mm, 100/pk	5183-4757-100
Column nut, collared, self-tightening, inlet/detector*	G3440-81011
20x Magnifier loop	430-1020

FID supplies for USP <467>

FID jet, universal fit, 0.29 mm (0.011 inch) id, capillary	5200-0176
FID jet, universal fit, 0.47 mm (0.018 inch) id	5200-0177

Pneumatic parts for USP <467>

1 mL Sample loop	G4556-80106
Sample probe, inert	G4556-63825

Transfer line connection for USP <467>

0.53 mm deactivated fused silica, 5 m	160-2535-5
1/6 to 1/32 inch reducing fitting	0100-2594
0.5 mm id short 85/15 Vespel/graphite, 10/pk*	5062-3514

Standards for USP <467> **

USP <467> class 2B low	5190-0513
USP <467> calibration standard	USPM-467C-1
USP <467> calibration standard	USPM-467A-1
USP <467> calibration standard	USPM-467D-1
USP <467> class 1 residual solvents	USPM-467J-1
USP <467> class 2 residual solvents A	USPM-467K-1
USP <467> class 2 residual solvents B	USPM-467L-1
USP <467> class 2 residual solvents B, low	USPM-467N-1
USP <467> class 2 residual solvents C	USPM-467M-1

Vials and septa for USP <467>

Headspace vial, crimp, clear, write-on spot, flat bottom, 20 mL, 23 x 75 mm, 100/pk	5190-2288
Headspace crimp cap 20 mm, high-performance septa, 100/pk	5190-3987

Crimper, decappers, 20 mm caps for USP <467>

A-Line E-crimper, for 20 mm caps	5191-5615
A-Line E-decapper, for 20 mm caps	5191-5613

Crimper, decapper accessories for USP <467>

Crimper jaw set, 20 mm	5190-4064
Decapper jaw set, 20 mm	5190-4065
Replacement lithium ion battery, for crimper	5190-3192

Keep your APIs free from toxic residual solvents—and increase confidence in your USP <467> results.

Visit www.agilent.com/chem/USP467solutions

*Supplies for 7890/8890 only.

**Not available in all countries. Please contact your local sales representative for availability.

Agilent CrossLab services. From insight to outcome.

CrossLab is an Agilent capability that integrates services and consumables to support workflow success and important outcomes like improved productivity and operational efficiency. Through CrossLab, Agilent strives to provide insight in every interaction to help you achieve your goals. CrossLab offers method optimization, flexible service plans, and training for all skill levels. We have many other products and services to help you manage your instruments and your lab for best performance.

Learn more about Agilent CrossLab, and see examples of insight that leads to great outcomes, at www.agilent.com/crosslab

Buy online:

www.agilent.com/chem/store

Find a local Agilent customer center in your country:

www.agilent.com/chem/contactus

U.S. and Canada

1-800-227-9770

agilent_inquiries@agilent.com

Europe

info_agilent@agilent.com

Asia Pacific

inquiry_lsca@agilent.com

This information is subject to change without notice.

© Agilent Technologies, Inc. 2020
Published in the USA, January 22, 2020
5991-8659EN
DE.5372685185

